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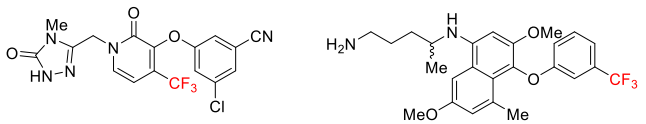
2,3,3,3-Tetrafluoropropene (HFO-1234yf) as a CF_3-building block: synthesis of enol ethers and vinyl sulfides

Ben J. Murray,[a] Ellis D. Ball,[a] Antal Harsanyi,[b] and Graham Sandford*[a]

Abstract: 2,3,3,3-Tetrafluoropropene (HFO-1234yf) is an inexpensive and readily available fluorinated building block, owing to its growing use as a low global warming potential 4th generation refrigerant, but there have so far been few reported uses of this fluoroalkene in organic synthesis. Here we report our investigations into nucleophilic substitution reactions of HFO-1234yf with alkoxide and thiolate derivatives. The regiochemistry of these transformations varies with conditions and we propose these reactions proceed via addition-elimination with reversible formation of a carbanion intermediate. The regioselectivity is dictated by hard/soft nucleophile/electrophile control. This is supported by deuterium trapping of the proposed reactive intermediate. The effect of solvent and base choice was examined and the substrate scope for the synthesis of α-trifluoromethyl enol ethers was expanded.

Introduction

The synthesis of trifluoromethylated compounds has long been of great importance in the pharmaceutical,[1] agrochemical[2] and materials science sectors.[3] Trifluoromethylation can impart many characteristics useful for drug molecules, such as improved metabolic stability and lipophilicity. Indeed, over 40% of NCEs (new chemical entities) approved by the FDA in 2018 were fluorinated and one third of these contained CF_3 groups.[4]



doravirine (Pifeltro™) *HIV/AIDS treatment*

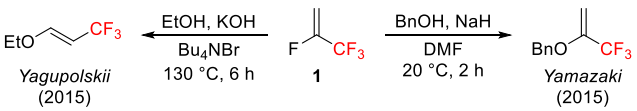
tafenoquine (Krintafel™) *anti-malarial*

Figure 1. Examples of CF_3-substituted therapeutic compounds approved by the FDA in 2018

Great strides have been made in recent years in the development of bench-stable trifluoromethylation reagents using various nucleophilic, electrophilic and radical systems.[5] However, many of these reagents have high associated costs and reduced atom economy when compared to HF and SF_4, from which they are ultimately derived. The introduction of trifluoromethyl groups on an industrial scale still largely relies on HF for halogen exchange (Swarts chemistry, $ArCCl_3$ to $ArCF_3$) or SF_4 in deoxofluorination ($ArCO_2H$ to $ArCF_3$) reactions. The use of inexpensive CF_3-containing building blocks, notably trifluoroacetic acid (TFA, derived from HF by electrolysis),[6] provides a compromise between these two approaches, removing the need for the user to handle highly toxic gaseous reagents whilst being low in cost and thus still suitable for reactions on process scale.

Thererefore, there still exists a need for new inexpensive CF_3-containing building blocks to increase access to diversely functionalised trifluoromethylated compounds. 2,3,3,3-Tetrafluoropropene (**1**, HFO-1234yf), has versatile synthetic potential, offering alternative routes to TFA derived syntheses. HFO-1234yf **1** is inexpensive and readily available as it is now used as a drop-in replacement for 1,1,1,2-tetrafluoroethane (HFC-134a) as the refrigerant in mobile air conditioning units for new vehicles in the EU. **1** is non-toxic and has relatively low flammability comparable to other refrigerant gases. Most importantly, **1** has an atmospheric lifetime of 10.5 days, compared to 13.4 years for HFC-134a, and so its global warming potential is 99.7% lower than that of its predecessor.[7]

Despite the ready availability of **1**, there have been very few reports of its use in organic synthesis as follows. Lu *et al*. demonstrated an oxidative Heck coupling of **1** with a range of boronic acids[8] whilst Ogoshi and co-workers developed copper-catalysed selective defluoroborylations[9] and silylations[10] for various fluoroolefins, including **1**. Work from the Crimmin group has recently described the reactions of **1** with aluminium complexes,[11] silyl lithium reagents[12] and boranes.[13] Braun and co-workers have also reported reactions of **1** with germanes[14] and rhodium complexes.[15] Of particular relevance to this study, two separate reports of nucleophilic substitution reactions of **1** with alcohols have been described (Scheme 1). Yamazaki *et al*. describe the *in situ* generation of sodium alkoxides in DMF from the respective alcohol and sodium hydride to give α-trifluoromethyl enol ethers.[16] In contrast, Yagupolskii *et al.* reported formation of the β-regioisomer using ethanol and potassium hydroxide at elevated temperatures.[17] No explanation for the differing results were discussed in these publications.



Yagupolskii (2015) — **1** — *Yamazaki* (2015)

Scheme 1. Previously reported reactions of **1** with alkoxides

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CF_3-substituted enol ethers, and equivalent vinyl sulfide systems, have the potential to be useful building blocks for a wide range of chemistry. However, they have thus far been underutilised in synthesis due to a lack of scaleable methods for their preparation. Related previous examples of the synthesis of trifluoromethyl enol ethers rely on Wittig[18] or Takai-Nozaki[19] olefinations of trifluoromethyl ketones or by addition of alkoxides to 3,3,3-trifluoropropyne[20] or bromotrifluoroalkenes.[21] The synthesis of trifluoromethyl vinyl sulfides has been carried out by the reaction of thiolates with trifluoromethylalkynes[22] or fluoro-,[23] chloro-[24] and bromo-trifluoromethylalkenes.[25] Other previously reported methods include Wittig olefination of trifluoromethyl thioesters[26] and copper-catalysed addition of TMS-CF_3 to the vinyl sulfide.[27] In this paper, we detail our investigations into preparation and mechanism for the synthesis of these useful CF_3-bearing building blocks from **1**, a much lower cost feedstock than those used previously in literature methods.

Results and Discussion

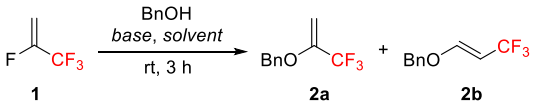
Yamazaki *et al*. reported that **1** reacted with benzyl alcohol to give the corresponding α-trifluoromethyl enol ether in quantitative yield but using pyrophoric NaH and toxic DMF. Alternative conditions more amenable to a manufacturing scale process were, therefore, sought. Firstly, the solubility of **1** in a range of common laboratory solvents was determined (Table 1).

Table 1. Solubility of **1** in various solvents as determined by ^{19}F NMR spectroscopy relative to an internal standard of α,α,α-trifluorotoluene

Solvent	Concentration of **1** / mmol dm^{-3}	Solvent	Concentration of **1** / mmol dm^{-3}
Water[a]	0.01	DCM	14.5
Ethanol	7.72	Ethyl acetate	23.5
2-Butanol	2.31	MeTHF	11.1
Acetic acid	26.1	MTBE	13.0
Acetonitrile	8.47	Toluene	8.32
DMSO	14.5	*p*-Cymene	4.60
Sulfolane	4.18	Triethylamine	7.02
DMF	21.7	Perfluorohexane	15.8
Acetone	12.5	Cyclohexane	6.12

[a] 2,2,2-trifluoroethanol was used as the internal standard

1 was found to be reasonably soluble in all solvents, except water, with polar aprotic solvents appearing to be the most effective. A range of bases and solvents were then screened for the reaction of **1** with benzyl alcohol (Scheme 2).



Scheme 2. Reaction of **1** with benzyl alcohol for screening of conditions

The products were identified based on the H-F coupling in the ^{19}F NMR spectra as the α- and β-trifluoromethyl enol ethers **2a** and **2b**. In the ^{19}F NMR spectrum of **2a** (Figure 2a), we observed a doublet with a small coupling constant of 2.0 Hz. The ^{1}H NMR spectrum of **2a** (Figure 2b) shows two peaks for the two inequivalent vinyl protons which couple to each other with a $^{2}J_{HH}$ value of 3.9 Hz. One of these proton signals also couples to the CF_3 group with a $^{4}J_{HF}$ value of 2.0 Hz, as seen in the ^{19}F NMR spectrum. ^{1}H-^{1}H NOESY spectroscopy reveals a through-space correlation between the vinylic proton that is coupled to the CF_3 group and the benzylic protons (Figure 2c). This demonstrates that the vinylic proton *trans* to the CF_3 group shows H-F coupling whereas the proton *cis* to the CF_3 group shows no H-F coupling.

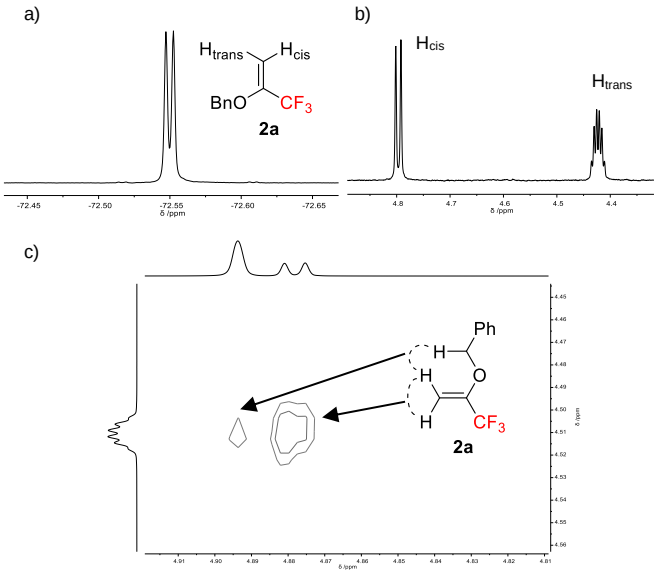


Figure 2. (a) ^{19}F NMR spectrum of **2a**; (b) ^{1}H NMR spectrum of **2a**; (c) ^{1}H-^{1}H NOESY spectrum of **2a** with key interaction highlighted

In some cases, the β-regioisomer **2b** was observed. This was identified on the basis of its ^{19}F NMR spectrum, showing a larger three-bond coupling with a $^{3}J_{HF}$ value of 8.3 Hz. This is corroborated by the ^{1}H NMR spectrum, where the vinylic protons couple to each other with a value of 6.9 Hz. Conversion of **1** to **2a** and **2b** was determined by comparison of the signals for the respective benzylic protons in the ^{1}H NMR spectra (Table 2).

Table 2. Screening of conditions for reaction of **1** with benzyl alcohol

Base	Solvent	% **2a**	% **2b**
KO^{t}Bu	DMF	29	10
NaO^{t}Bu		19	3
NaHMDS		80	0
Cs_2CO_3		0	0
NaH	THF	42	0
	MeTHF	13	0
	DMA	100	0
	NMP	98	0
	DMSO	100	0
	Acetonitrile	97	3
	Propylene carbonate	39	0

The possibility of forming the alkoxide substrate beforehand instead of *in situ* was also considered but no reaction was observed between **1** and NaOEt in DMF so this option was not pursued further. Of all the bases trialled, only NaHMDS was found to be a viable alternative to NaH.

The relatively poor solubility of **1** in THF and MeTHF is believed to be the reason for the low conversions in these solvents. Polar aprotic solvents are clearly the best options with DMA and DMSO both showing complete conversion to the product enol ether. Propylene carbonate showed significant transesterification and, therefore, was not a viable solvent.

Overall, we confirmed that Yamazaki's conditions of DMF and NaH gave highest conversion. The synthesis of **2a** was successfully carried out on a 20 gram scale using a simple rubber gas bladder (see SI for image of set-up). The reaction remained entirely regioselective for the α-regioisomer. By using **1** in a large excess with respect to benzyl alcohol, **2a** could be isolated in excellent yield with the only purification needed being an aqueous workup and filtration through Celite.

We then sought to explore the limitations of the substrate scope of this α-trifluoromethyl enol ether synthesis (Scheme 3). As before, the only purification needed in most cases was a simple filtration followed by aqueous workup. Pyridinyl (**3b**), piperonyl (**3c**) and cyclopropanyl (**3f**) cyclic systems were all well tolerated, as were furanyl and imidazolyl rings although with lowered yields of enol ethers **3h** and **3i**, respectively. This can be attributed to the volatility of the products rather than any chemical incompatibility. Benzyl-protected sugar **3j** appeared to break down under these conditions to form benzyl alcohol, which then reacted with **1** to give **2a** cleanly.

The presence of an activated chloride functionality had no deterimental impact on the yield of **3b**. Free amines were tolerated but gave significantly reduced yield of enol ether **3k** due to reaction with DMF. With 2-hydroxyacetophenone (**3g**), competing side reactions involving enol formation were observed under these basic conditions and this led to formation of an intractable complex mixture. While **3e** was expected to be unreactive at the phenolic site, it was also suprisingly unreactive at benzylic alcohol positions. Amine and amide substrates **3l-o** were unsuccessful as the corresponding alkoxides had poor solubility in DMF and so negligible conversion was obtained in all four cases.

Reaction of **1** with 2-naphthalenemethanol afforded a crystalline product (**3a**) and so gave unequivocal confirmation of regioselectivity by X-ray crystallography (Figure 3).

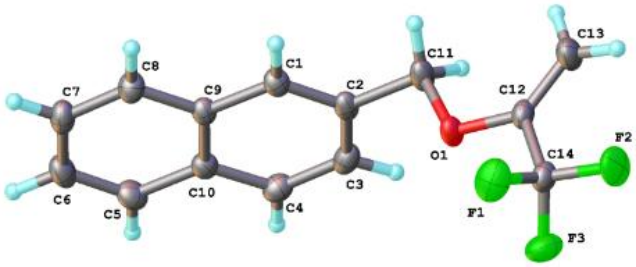
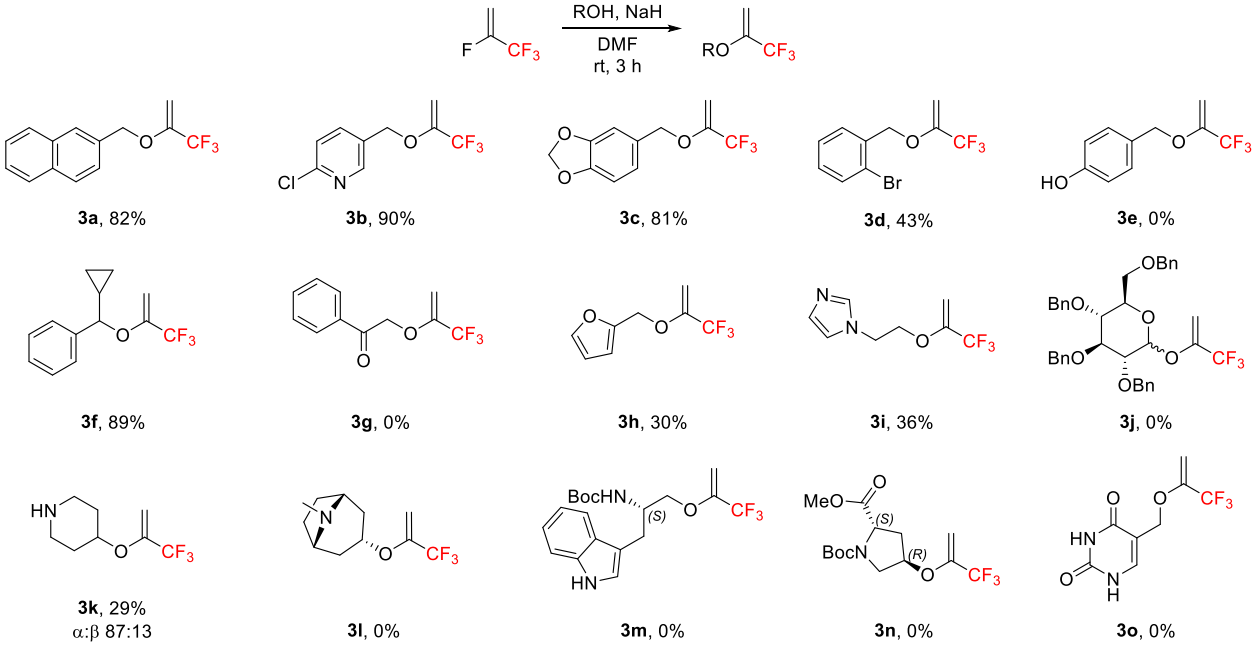


Figure 3. Molecular structure of **3a** as determined by X-ray crystallography



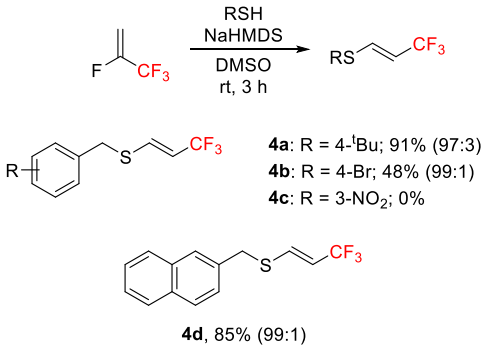
Scheme 3. Substrate scope for synthesis of α-trifluoromethyl enol ethers from **1** with isolated yields; all products 100% α-regioisomer unless otherwise stated

We were interested in the stability of these potentially useful building blocks. A range of hydrolysis conditions for enol ether systems were attempted with **3a** and it proved remarkably resilient towards Brønsted acids and bases (Table 3). Mild oxidation with $(NH_4)_2Ce(NO_3)_6$ (CAN) also showed no change. Only treatment with the mild Lewis acid $La(OTf)_3$ showed any reaction, with formation of 1,1,1-trifluoroacetone detected by ^{19}F NMR spectroscopy and and 2-naphthalenemethanol by GC-MS. The use of a stronger Lewis acid, $BF_3.OEt_2$, gave only 13% conversion on the same timescale. However, $BF_3.OEt_2$ was used under anhydrous conditions whereas $La(OTf)_3$ can be used in aqueous media. Both water and a Lewis acid, therefore, appear to be neccessary for the decomposition of **3a** via this mechanism.

Table 3. Screening of conditions for deprotection of **3a** at room temperature (approximately 20 °C) with conversion determined by ^{19}F NMR spectroscopy

Reagent	*t* / hrs	% Conversion
HCl (37%)	48	0
HBr (48%)	4	0
HI (55%)	4	0
$(CO_2H)_2$	48	0
PTSA	16	0
CAN	16	0
$La(OTf)_3$	4	83
Cs_2CO_3	48	0
NaOH	48	0
KF	48	0
DBU	48	0

Under the same conditions as the reaction of **1** with benzyl alcohol, the equivalent thiolate formed from sodium hydride and benzyl thiol gave an intractable complex mixture of vinyl sulfides, sulfoxides, sulfones and thioacetals. However, by using two equivalents of NaHMDS in DMSO, clean conversion to the β-trifluoromethyl vinyl sulfide **4a** was achieved with complete regioselectivity and excellent *E*:*Z* stereoselectivity (Scheme 4). For the major stereoisomer, a $^3J_{HF}$ three-bond H-F coupling of 8.5 Hz and a four-bond H-F coupling with a $^4J_{HF}$ value of 1.0 Hz was observed in the ^{19}F NMR spectrum of **4a** (Figure 4a). By contrast, for the minor stereoisomer $^3J_{HF}$ was 6.2 Hz and $^4J_{HF}$ was 2.0 Hz (Figure 4b). The precedent of **2a** discussed above shows that there is a greater coupling between the fluorine of the CF_3 group and the *trans* vinylic protons than to the *cis*. The smaller four-bond coupling for the major stereoisomer of **4a**, therefore, implies that the reaction is selective for the *E* stereoisomer. As with the alcohol reactions above, the products were isolated in good yield and purity without the need for column chromatography. The reaction was then expanded to a range of other benzylic thiols (**4b**-**d**).



Scheme 4. Synthesis of β-trifluoromethyl vinyl sulfides from **1** with isolated yields (and *E*:*Z* ratios)

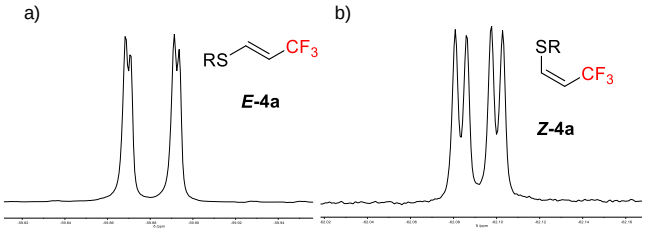
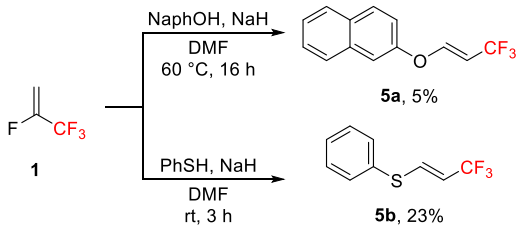


Figure 4. (a) ^{19}F NMR spectrum of *E*-**4a**; (b) ^{19}F NMR spectrum of *Z*-**4a**

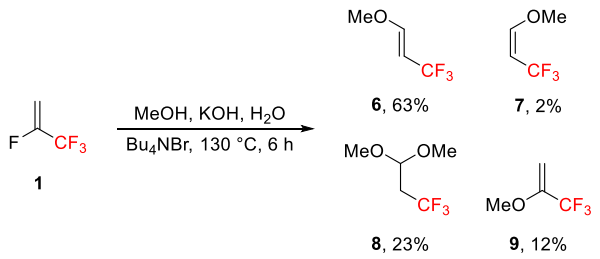
Phenol was reported by Yamazaki *et al.* to be unreactive with **1** at room temperature. However, at 60 °C, we found that **1** and 2-naphthol reacted in DMF with sodium hydride, albeit giving very low conversion to enol ether **5a** (Scheme 5). Only the *E*-stereoisomer of the β-regioisomer was obtained, suggesting a similar mechanism to the reaction with thiols. Thiophenol was unreactive under the standard conditions for thiols described above but did react at room temperature using sodium hydride. The same stereo- and regioselectivity was observed as for 2-naphthol but with improved conversion owing to its increased nucleophilicity, although the isolated yield of vinyl sulfide **5b** remained fairly low.



Scheme 5. Reactions of **1** with sodium 2-naphthoyloxide and thiophenolate

Our work on the reactions of **1** with nucleophiles was prompted by our interest in the different regioselectivies reported in the literature. Having confirmed the reports of Yamazaki *et al.*, repetition of the reported synthesis of the β-trifluoromethyl regioisomer by Yagupolskii *et al*. was attempted. Using protic conditions, a complex range of products was obtained (Scheme

6). To facilitate the high temperatures and pressures required, the reaction was carried out in a sealed glass Carius tube.



Scheme 6. Reaction of **1** with methanol under Yagupolskii's conditions with product composition given as determined by NMR spectroscopy

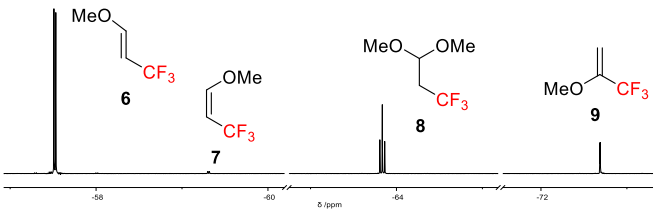
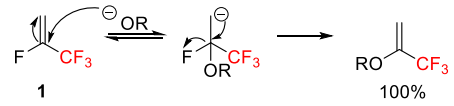


Figure 5. ^{19}F NMR spectrum from reaction of **1** with methanol and potassium hydroxide at 130 °C

The products obtained were identified by their ^{19}F NMR spectrum (Figure 5). The major product was the (*E*)-β-regioisomer **6**, with the stereochemistry assigned as discussed above. Some *Z*-stereoisomer, **7**, was also produced. However, the ^{1}H NMR signals for **6** or **7** could not be unequivocally identified due to overlap with other peaks. Overall, 97% of the β-regioisomer that formed was **6** with only 3% **7**. Some acetal formation, **8**, was also observed, as reported by Yagupolskii previously.

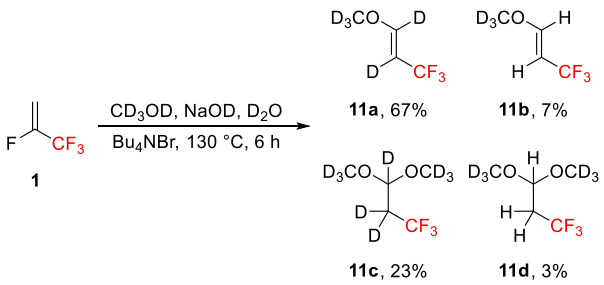
α-Regiosiomer, **9**, was also formed for which the ^{19}F and ^{1}H NMR peaks had identical splitting to those observed above. While there was no reported synthesis of the α-regioisomer by Yagupolskii, the crude reaction mixture was directly subjected to acid hydrolysis to form 3,3,3-trifluoropropanal from **6**, **7** and **8**. Under these conditions, **9** would be converted to the highly volatile 1,1,1-trifluoroacetone and so could have been removed during purification of the aldehyde without being detected. Overall, 85% of the enol ether formed was the β regioisomer with 15% being the α. These results demonstrate that both of the original reports in the literature are accurate, although neither paper discusses the reasons for the regioselectivities obtained.

We propose that these reactions proceed via an addition-elimination nucleophilic vinylic substitution process similar to those that are well established for reactions of other CF_3-substituted alkenes.[28] Nucleophilic attack can occur at one of two positions, leading to formation of two possible carbanions. Each is stabilised by the electron-withdrawing fluorine atoms in the system and reactions of polyfluorinated alkenes have often been observed to proceed via such intermediates.[29] Under aprotic conditions (Scheme 7), direct substitution of fluorine can occur by attack of the hard alkoxide nucleophile at the 'hard' site of the carbon-carbon double bond.



Scheme 7. Mechanism for reaction of **1** with hard nucleophiles, such as alkoxides under aprotic conditions

Under protic conditions, alkoxides are softer nucleophiles due to solvation so nucleophilic attack occurs at both the hard and soft sites of the double bond in competition. To support these conclusions, reaction of **1** with methanol-d_4 and NaOD was carried out and gave a mixture of compounds (**11a-d**) with varying degrees of deuterium incorporation (Scheme 8). The ^{1}H NMR spectrum showed no vinylic protons in the expected region and the CF_3 resonances in the ^{19}F NMR spectrum were observed as singlets (Figure 6). This confirms that deuterium has been incorporated in both possible vinylic positions, which confirms that nucleophilic attack occurs at both sp^2 carbon sites and that formation of the carbanion intermediate is reversible (Scheme 9).



Scheme 8. Reaction of **1** with methanol-d_4 and sodium deuteroxide with conversion determined by NMR spectroscopy

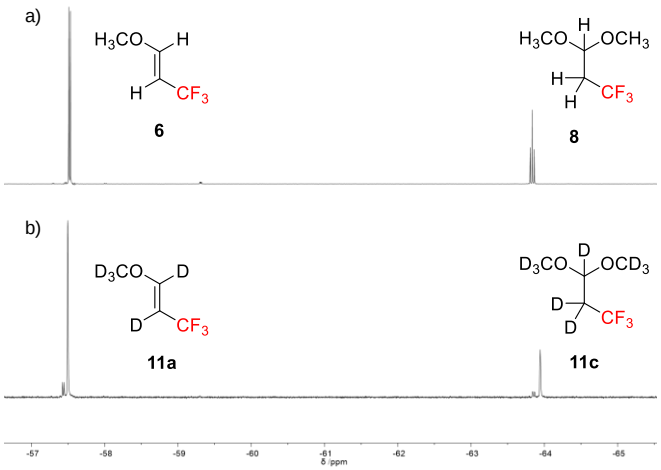
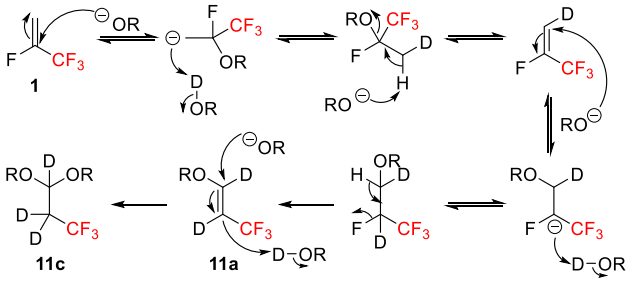


Figure 6. ^{19}F NMR spectra from reaction of **1** with $CH_3OH/KOH/H_2O/Bu_4NBr$ (top) and $CD_3OD/NaOD/D_2O/Bu_4NBr$ (bottom) at 130 °C for 6 hours

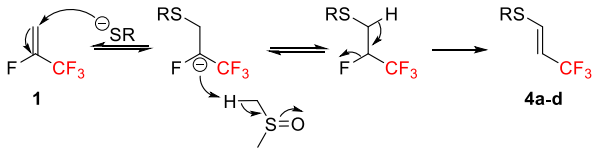


Scheme 9. Mechanism for deuterium incorporation into **11a** and **11c**

The β-trifluoromethyl enol ether can exist as either of the *E*- and *Z*-stereoisomers, with the stereochemistry of the product determined by the conformation of the protonated intermediates. The intermediate that would lead to the *Z*-isomer **7** involves steric clash between the CF_3 and OR groups whereas there is less hindrance in the more favoured conformation that gives the *E*-isomer **6**. This matches the stereoselectivity observed above (Scheme 6). By contrast, selective formation of the *Z*-stereoisomer was reported when reacting 2-bromo[30] and 2-chloro-3,3,3-trifluoropropene[31] with alkoxides. In these cases, the reaction instead proceeds via elimination of HBr or HCl to give an alkyne intermediate to which the alkoxide then reacts. The different configuration under protic conditions suggests an alkyne intermediate is not formed from **1**.

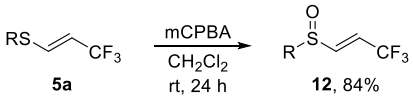
This mechanism also explains why some β-trifluoromethyl regioisomer was obtained in the synthesis of **3k**, as the free amine could act as a proton source and so protonate the carbanion intermediate leading to the β regioisomer, which would usually be inaccesible under aprotic conditons.

For reaction of **1** with thiolates, nucleophilic attack by the softer nucleophile occurs at the softer alkene site. The intermediate carbanion is then protonated and eliminates HF to give the vinyl sulfide product via an E2 elimination process. The *E*-stereoisomer would be expected to be the major product due to there being less steric hindrance in the conformation of the protonated intermediate leading to this product (Scheme 10) as observed in the synthesis of **4a**-**d**, with *E*:*Z* selectivities of up to 99:1.



Scheme 10. Mechanism for reaction of **1** with soft nucleophiles, i.e. thiolates

Oxidation of **4a** to give the corresponding sulfone was attempted as such an electron-poor alkene would be a highly reactive building block in, for example, Diels-Alder reactions. However, the use of Oxone®, mCPBA and hydrogen peroxide gave only sulfoxide **12**, as evidenced by mass spectrometry. Stronger oxidising reagents, such as potassium permanganate, gave intractable complex mixtures of products. Nevertheless, **12** was obtained in a high yield using mCPBA (Scheme 11) and could be a useful building block for a wide range of chemistry in its own right.



Scheme 11. Oxidation of vinyl sulfide **5a** to give sulfoxide **12**; R = 4-(*tert*-butyl)benzyl

Conclusions

A range of α-trifluoromethyl enol ethers were synthesised in generally good yields and minimal purification. In contrast, thiols and softer oxygen centred nucleophiles, such as naphthols, gave products with opposite regioselectivity.

Our investigation into the mechanism of the reaction of HFO-1234yf with oxygen and sulfur nucleophiles confirms that the regioselectivity of the nucleophilic addition-elimination mechanism depends on reaction conditions and nature of the nucleophile. Hard nucleophiles in aprotic media attack the hard sp^2 carbon giving products arising from addition-elimination of the vinyllic fluorine atom. Alkoxides in protic media are softer nucleophiles and give products derived from attack at both hard and soft sp^2 carbon atoms of HFO-1234yf while soft nucleophiles give products arising from selective attack at the CH_2 group of HFO-1234yf. The resulting enol ether and vinyl sulfide building blocks have great potential to access a wide range of CF_3-substituted structures.

Experimental Section

General procedure: α-trifluoromethyl enol ether synthesis. NaH (60% suspension in mineral oil, 1.5 equivalents) under an argon atmosphere was washed with hexane then anhydrous DMF was added. The alcohol (as a solution in anhydrous DMF if alcohol solid at room temperature, 1 equivalent) was added dropwise at 0 °C then stirred at room temperature for 30 minutes. The resulting alkoxide solution was then stirred under an atmosphere of **1** (excess), introduced via a gas bladder. The reaction mixture was stirred at room temperature for 3 hours, unless otherwise indicated, then carefully quenched with saturated aqueous ammonium chloride and filtered through a Celite plug, which was then washed with ethyl acetate. The aqueous phase was extracted with ethyl acetate then the combined organic extracts were washed twice with 0.5 M HCl then with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give the α-trifluoromethyl enol ether product without further purification unless otherwise specified.

2-Benzyloxy-3,3,3-trifluoroprop-1-ene (2a). Following the general procedure, benzyl alcohol (12.5 g, 0.116 mol), **1** (25.5 g, 0.224 mol) and NaH (7.95 g, 0.331 mol) in DMF (250 mL) gave 2-benzyloxy-3,3,3-trifluoroprop-1-ene, **2a** (20.8 g, 89%), as a colourless oil. δ_H (400 MHz; $CDCl_3$) 4.53 (1H, dt, $^2J_{HH}$ 3.9, $^4J_{HF}$ 1.9, H_{trans}), 4.90 (1H, d, $^2J_{HH}$ 3.9, H_{cis}), 4.91 (2H, s, CH_2), 7.40 (5H, m, Ph). δ_F (376 MHz; $CDCl_3$) −72.42 ($^4J_{HF}$ 1.9). δ_C (101 MHz; $CDCl_3$) 70.63, 88.39 (q, $^3J_{CF}$ 3.6), 119.96 (q, $^1J_{CF}$ 273.3), 127.46, 128.47, 128.78, 135.39, 150.28 (d, $^2J_{CF}$ 34.6). IR ν_{max} /cm^{-1} 2922, 2853, 1656, 1457, 1377, 1347, 1195, 1153, 1028. GC-MS (EI+) *m*/*z* 202 ([M+H]$^+$, 6%), 92 ([Bn+H]$^+$, 95), 91 (Bn$^+$, 100), 65

($C_5H_5^+$, 51), 39 ($C_3H_3^+$, 15). HRMS (ASAP, AI+) M^+ *m/z* 201.0530; calc. for $C_{10}H_8OF_3$ 201.0527.

General procedure: β-trifluoromethyl vinyl sulfide synthesis. The thiol (1 equivalent) was dissolved in anhydrous DMSO under an argon atmosphere then NaHMDS (2M in THF, 2 equivalents) was added dropwise and the resulting mixture stirred at room temperature for 30 minutes. The reaction mixture was stirred under an atmosphere of **1** (excess) provided via gas bladder for 3 hours then carefully quenched, filtered and subjected to aqueous workup as for the enol ethers described above to give the crude product without further purification unless otherwise specified.

(*E*)-1-(4-(*tert*-Butyl)benzyl)thio-3,3,3-trifluoroprop-1-ene (4a). Following the general procedure, 4-(*tert*-butyl)benzyl mercaptan (0.498 g, 2.75 mmol), **1** (1.65 g, 14.5 mmol) and NaHMDS (2.5 mL, 5.0 mmol) in anhydrous DMSO (15 mL) gave (*E*)-1-(4-(*tert*-butyl)benzyl)thio-3,3,3-trifluoroprop-1-ene, **4a** (0.688 g, 91%) as a yellow oil. δ_H (400 MHz; $CDCl_3$) 1.36 (9H, s, ^{t}Bu), 3.97 (2H, s, CH_2), 5.57 (1H, dq, $^2J_{HH}$ 11.0, $^3J_{HF}$ 8.5, C(2)H), 6.69 (1H, dq, $^2J_{HH}$ 11.0, $^4J_{HF}$ 1.0, C(1)H), 7.29 (2H, m, ArH), 7.41 (2H, m, ArH). δ_F (376 MHz; $CDCl_3$) −59.88 (dd, $^3J_{HF}$ 8.5, $^4J_{HF}$ 1.0). δ_C (101 MHz; $CDCl_3$) 31.42, 34.69, 60.54, 112.88 (q, $^2J_{CF}$ 35.0, C2), 123.60 (q, $^1J_{CF}$ 270.9, CF_3), 125.95, 128.79, 133.45, 138.72 (q, $^3J_{CF}$ 5.1, C1), 150.92. IR ν_{max} /cm^{-1} 2963, 1737, 1615, 1516, 1464, 1364, 1268, 1203, 1111, 1047, 1018. GC-MS (EI+) *m/z* 274 (M^+, 17%), 147 (100, ^{t}BuPhCH$_2^+$), 117 (40, ^{i}PrPh$^+$), 105 (25, PhMe$_2^+$), 91 (19, Bn$^+$). HRMS (ESI+) *m/z* calc. for $[M+MeCN]^+$ $C_{16}H_{20}F_3NS$ 315.1269; found 315.1037.

Full characterisation data for all compounds is given in the SI. Crystallographic data for **3a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC-1947946.

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Keywords: fluorine • organofluorine compounds • trifluoromethyl • HFO-1234yf • enol ethers

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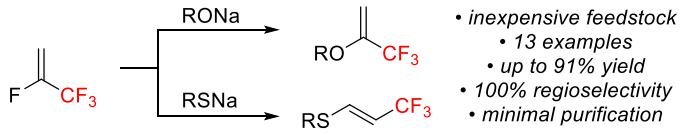

2,3,3,3-Tetrafluoropropene is an inexpensive and readily available 4th generation refrigerant. Reaction with alkoxides and thiolates gives α-CF_3 enol ethers and β-CF_3 vinyl sulfides, respectively, with complete regioselectivity.

Key Topic: Organofluorine Chemistry

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2,3,3,3-Tetrafluoropropene (HFO-1234yf) as a CF_3-building block: synthesis of enol ethers and vinyl sulfides